# SUBLINGUAL FENTANYL SPRAY

This application claims the benefit of U.S. Provisional Patent Application Nos. 60/963,076, filed on Aug. 2, 2007 and 60/963,253 filed Aug. 3, 2007; the disclosures of which are hereby incorporated by reference in their entireties.

## FIELD OF THE INVENTION

The invention is directed to sublingual formulations containing fentanyl, a pharmaceutically acceptable salt thereof, or derivative thereof, suitable for administration to humans, and methods for treatment with the sublingual formulations.

## BACKGROUND OF THE INVENTION

Fentanyl is a μ-opioid receptor agonist with analgesic potency approximately 80-100 times that of morphine. In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. Its primary actions are analgesic and sedation.

The analgesic effects of fentanyl are related to the blood level of the drug. In general, the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance to any and all opioids. The rate of development of tolerance may vary widely among individuals. All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is typically less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. Serious or fatal respiratory depression can occur, even at recommended doses, in vulnerable individuals.

Orally administered fentanyl is subject to first pass effect metabolism as upwards of 50% or more of orally administered fentanyl is not absorbed. Other forms of delivery such a parenteral, buccal, and transdermal have been utilized to decrease or avoid this first pass effect for fentanyl.

Fentanyl is currently available in injectable form, as a lozenge (e.g. Actiq®), and as a transdermal system (e.g., Duragesic® 25, 50, 75, and 100 μg of fentanyl per hour). Duragesic® provides continuous systemic delivery of fentanyl for approximately 72 hours. Duragesic® is indicated in the management of chronic pain in patients requiring continuous opioid analgesia for pain that is not optimally managed with lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or prn (as needed) dosing with short-acting opioids. Duragesic® is typically not suitable for patients experiencing acute pain due to the delay in absorption of the fentanyl through the patch, or postoperative pain because serious or life-threatening hypoventilation could result.

Actiq® is a solid formulation of fentanyl citrate, intended for oral transmucosal administration. Actiq® is a lozenge attached to a handle similar in shape to a lollipop. The handle is purportedly to allow the Actiq® unit to be removed from the mouth if signs of excessive opioid effects appear during administration. Actiq® is indicated for the management for breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Actiq® is contraindicated in the management of acute or postoperative pain.

Sublingual tablets and lozenges (e.g., Actiq®) which may be used for acute pain or breakthrough pain have certain disadvantages. A disadvantage, amongst others, is that after intake the active agent in these pharmaceutical agents must first be released and dispersed prior to being available for resorption in dissolved form. In addition, the absorption pharmacokinetics of fentanyl from Actiq® may vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed. Further, certain lozenges may be in the form of a candy which require medical supervision and may be socially questionable.



There exists a need in art for a sublingual formulation including fentanyl, a pharmaceutically acceptable salt thereof, or derivative thereof, which is suitable for effective pain management.

## SUMMARY AND OBJECTS OF THE INVENTION

It is an object of the invention to provide a fentanyl formulation suitable for sublingual administration for effective pain management.

It is an object of certain embodiments of the invention to provide methods and compositions capable of rapidly inducing a state of sedation, analgesia, and/or anesthesia.

It is a further object of certain embodiments of the invention to provide methods and compositions for fentanyl administration which minimize the underdosing and/or overdosing of a patient in need of fentanyl therapy.

It is a further object of certain embodiments of the invention to provide methods and compositions suitable for the treatment of breakthrough pain in patients receiving chronic pain treatment.

It is a further object of certain embodiments of the present invention to provide a method for sublingual administration of fentanyl, a pharmaceutically acceptable salt thereof, or derivative thereof, in a controlled amount for the treatment of pain.

It is a further object of certain embodiments of the present invention to provide a dosage form of an opioid analgesic which can be administered sublingually in a manner which will cause substantial sublingual absorption without substantial risk of the dose passing into the lungs of the recipient.

The above-mentioned objects and others are achieved by virtue of the present invention, which is directed in part to a method for sublingually administering fentanyl, a pharmaceutically acceptable salt thereof, or derivative thereof, to provide fast-acting relief in a formulation in which a substantial portion of the fentanyl, a pharmaceutically acceptable salt thereof, or derivative thereof will not be passed into the lungs of the patient.

In certain embodiments the present invention is directed to a sublingual fentanyl formulation comprising discrete liquid droplets comprising an effective amount of fentanyl, a pharmaceutically acceptable salt thereof, or derivative thereof, said droplets having a mean diameter of at least about 10 microns, preferably at least about 20 microns, more preferably a mean diameter of from about 20 to about 200 microns.

In certain embodiments, the present invention is directed to a sublingual fentanyl formulation comprising discrete liquid droplets of fentanyl, a pharmaceutically acceptable salt thereof, or derivative thereof; in a pharmaceutically acceptable liquid carrier; said droplets having a size distribution of from about 5 microns to about 500 microns, preferably from about 10 microns to about 200 microns, preferably from about 20 microns to about 100 microns, more preferably from about 30 microns to about 70 microns.

In certain preferred embodiments, none of the particles have a diameter which would allow the fentanyl, pharmaceutically acceptable salt thereof, or derivative thereof to be delivered to the lung upon sublingual administration.